REMARKS/ARGUMENT

The specification has been objected to and the claims rejected under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure and the claims have been further rejected under the second paragraph of Section 112 as being indefinite. This objection and rejections are predicated on the reference in the claims to "Selective Estrogen Receptor Modulator", the alleged reference in the claims to an "agent(s) which exhibits progestogenic activity (which) is effective to modulate the side effects of the Selective Estrogen Receptor Modulator" and based on the assertion that criteria defining such materials were not set forth in the application while "only a limited number" of these materials are set forth "thereby failing to provide sufficient working examples". Reconsideration is respectfully requested. It is respectfully submitted that, taking into consideration the factors listed on page 3 of the Office Action, no undue experimentation is required and the claims are definite.

The specification indicates on page 5 that any known SERM, the acronym for a Selective Estrogen Receptor Modulator, can be used in the present invention and then proceeds over the course of approximately two pages to give specific examples of known SERMs. It is respectfully submitted it is a mischaracterization of the disclosure to say that "only a limited number" of specific examples are set forth.

Applicant previously pointed out that both the acronym SERM and the full name Selective Estrogen Receptor Modulator are well known and well understood in the art. In this connection, attached hereto as Appendices A and B are excerpts from literature and issued U.S. patents which demonstrate this fact. What constitutes a SERM is clear and definite to those of ordinary skill in this art.

As to the other agent, it should first be recognized that the Office Action language does not accurately reflect the term actually used in the claims. The claims do <u>not</u> recite an "agent which exhibits progestogenic activity which is effective to modulate the side effects of the Selective Estrogen Receptor Modulator". Instead, they call for an "agent which exhibits progestogenic activity". The recitation "effective to modulate the side effects of the Selective Estrogen Receptor Modulator" refers to the amount employed and does not represent an effort to

create a subcatagory of progestogenic agents, as might be implied from the text of the Office Action. The application discloses that the "agent which exhibits progestogenic activity" can be progesterone, a synthetic progestin analogue or even an anti-progestin having antagonistic activity and then proceeds over approximately a page to give specific examples. What constitutes a progestogenic agent is clear and definite to those of ordinary skill in this art.

Beyond the foregoing, the application sets forth a variety of examples of suitable combinations of agents which exhibit progestogenic activity with SERMs. The quantity of experimentation required based on the amount of direction or guidance provided in the application, the presence of the working examples and extensive descriptions, the nature of the invention, the state of the art, and the skill of those of the art, is hardly undue.

Withdrawal of the objection and rejections under 35 U.S.C. § 112 is respectfully solicited.

The claims have been rejected under 35 U.S.C. § 103 over Jones, Basu and Schane. This rejection is respectfully traversed.

What is claimed in the present application is a method of achieving conception in a pre-menopausal female by administering a contraceptively effective amount of a combination of a SERM and a progestogenic agent, where, in addition, the amount of the agent is effective to modulate the side effects of the SERM.

The Schane Chemical Abstract refers to the use of danzole, a progestogenic agent, as an oral contraceptive in the rhesus monkey.

The other references have been cited to show the use of SERMs to establish contraception. In considering these references, it should be kept in mind that these references are dated in the 1970's. That fact is significant because while the cited references reflect the early thinking with regard to SERMs as anti-fertility agents, they do not reflect reality. SERMs, when used in premenopausal women as claimed in this application, are fertility agents, not anti-fertility agents. Clomiphene was originally believed to have a potential use as a contraceptive agent but in human trials, its use resulted in pregnancies and not contraception. In this connection, the Examiner's attention is respectfully invited to the attached pages from the Clark and Mani text, Actions of Ovarian Steroid Hormones, in The Physiology of Reproduction, and Glass, Fertility,

in Reproductive Endocrinology. Attention is particularly invited to page 1041 of Clark which indicates that clomiphene and a closely related analogue

> were initially described as inhibitors of gonadotropin secretion in the rat and were considered to be likely candidates for agents that would block fertility. However, when they were tried in women, the opposite situation was observed. This difference between the effects of clomiphene in the rodent and human may be due to species differences; however, it is more likely to be due to differences in treatment protocols. . . . As pointed out by Docke, the cycling rat is not comparable to an ovulatory woman . . . In humans, clomiphene induces ovulation in anovulatory women . . . . (references omitted).

It will therefore be appreciated that as to human beings, and more particularly, premenopausal women, SERMs are not contraceptive agents. Further with regard to the Jones reference, it should be recognized that it is an abstract of U. S. Patent 4,133,814, a copy of which is attached hereto, and as is clear from columns 9 and 32 thereof, the "anti-fertility" activity in this reference is with respect to birds, rodents and small animals such as coyotes, foxes, etc.

The Office Action asserts that the idea for combining the prior art flows logically from the individual materials having been used for the same purpose in the prior art. However, as discussed above, the SERMs in the present invention are not being used for an anti-fertility effect, and those skilled in the art would know that a SERM has a fertility effect and not an anti-fertility effect. Therefore, the predicate for the asserted obviousness, use for the same purpose, is absent.

The Applicant is combining the progestin with a fertility agent (the SERM) to achieve contraception and, in addition, the progestin modulates the side effects of the SERM. The present invention seeks to take advantage of the SERM's positive estrogenic effects and it is the combination of the SERM and the progestin which results in the contraceptive effect. It will be further noted that there is nothing in the art cited which suggests that the progestin is effective to modulate the side effects of the SERM.

In light of the foregoing considerations, it is respectfully submitted that the prior art rejection should be withdrawn.

The early issuance of a Notice of Allowance is respectfully solicited.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Asst. Commissioner for Patents, Washington, D.C. 20231, on August 27, 2001:

Edward A. Meilman
Name of applicant, assignee or Registered Representative

Signature

August 27, 2001
Date of Signature

EAM:mcm:swu:mgs
Enclosures

Respectfully submitted,

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Appendix A

Selective estrogen receptor modulators (SERMs) exhibit a pharmacologic profile characterized by estrogen agonist activity in some tissues with estrogen antagonist activity in other tissues. DB Muchmore, The Oncologist.

Selective oestrogen receptor modulators (SERMs) are compounds which act like oestrogens in some target tissues but which antagonize their effects in others. HG Burger, Hormone Research.

SERMs constitute a new classification of estrogen product – a "designer estrogen" that will hopefully furnish all the benefits of estrogen (reducing the risk of both heart disease and osteoporosis and perhaps protecting from dementia) without the known drawbacks (increasing the risk of both endometrial cancer and breast cancer). J O'Leary-Cobb.

Tamoxifen, a selective estrogen receptor modulator.....Raloxifene is another SERM ... RM O'Regan and VC Jordan Semin Oncol.

SERMs have many potential uses, and are currently approved for use by women with breast cancer (tamoxifen, toremifene).... DB Muchmore, The Oncologist.

Raloxifene: A selective estrogen receptor modulator.... DB MUCHmore, The Oncologist.

Levormeloxifene, a nonsteroidal selective estrogen receptor modulator (SERM)...CE Hotchkiss et al, Bone.

Ospemifene is a novel selective estrogen receptor modulator....TL Taras et al, J Steroid Biochem Mol Biol

Idoxifene is a tissue-specific selective estrogen receptor modulator. T Omoya et al, Liver.

Centchroman, a selective estrogen receptor modulator... MM Singh, Med RES Rev.

Appendix B

United States Patent **6,132,774**

Ke , et al. **October 17, 2000**

Title: Therapeutic combinations comprising a selective estrogen receptor modulator and parathyroid hormone

"This invention relates to a pharmaceutical combination of a selective estrogen receptor modulator (***SERM***) and parathyroid hormone (PTH) or a biologically active fragment thereof that stimulates bone formation, increases bone mass and enhances bone restoration effects of PTH."

United States Patent **6,077,852**

Bales , et al. **June 20, 2000**

Title: Treatment of central nervous system disorders with selective estrogen receptor modulators

"The compounds of the present invention are selective estrogen receptor modulators (***SERM's***), that is, compounds which produce estrogen agonism in one or more desired target tissues while producing estrogen antagonism and/or minimal (i.e. clinically insignificant) agonism in reproductive tissue such as the breast or uterus."

United States Patent **5,994,370**

Bryant , et al. **November 30, 1999**

Title: Indene compounds having activity as SERMS

"The present invention provides a class of substituted indene compounds and their pharmaceutically acceptable salts which possess selective estrogen receptor

modulator (SERM) activity and are thus useful in the treatment of osteoporosis and cardiovascular disease, particularly hyperlipidemia in women...."

"As a consequence, there is a need for the development of postmenopausal therapy agents which possess the ideal pharmacological profile: for example agents which produce the beneficial effects of estrogen upon vasomotor systems, skeletal tissue and the cardiovascular system without producing the adverse effects of estrogen upon reproductive tissues. Agents possessing such an estrogen profile would reverse the effects of estrogen deficiency in certain tissues while at the same time bypassing or failing to act in tissues in which estrogen produces adverse effects. The term selective estrogen receptor modulators or "SERMs" has been applied such compounds which possess this tissue selective profile. SERMs are defined as compounds producing estrogen agonism in one or more desired target tissues such as bone, liver, etc., together with estrogen antagonism and/or minimal (i. e. clinically insignificant) agonism in reproductive tissues such as the breast or uterus."

United States Patent **5,977,383**

Vicenzi , et al. **November 2, 1999**

Title: Process for the synthesis of benzothiophenes

"Benzothiophene is a key intermediate in the synthesis of raloxifene, a selective estrogen receptor modulator, or ***SERM***."

United States Patent **6,262,098**

Huebner , et al. **July 17, 2001**

Title: Estrogen receptor modulators

"More particularly, the present invention provides selective estrogen receptor modulators ("SERMs")."

"However, the discovery that some agents acted as estrogen agonists in some tissues (e.g., bone) and as an antagonists in other tissues (e.g., breast) provided hope that more effective treatments for estrogen loss could be found (Gradishar and Jordan 1997; Gustafsson 1998; Jordan 1998; MacGregor and Jordan 1998). The best known of these so-called Selective Estrogen Receptor Modulators ("SERMs"), tamoxifen, has been demonstrated to have therapeutic utility in treating and preventing breast cancer and lowering LDL concentrations; yet, without significant reduction bone density (Jordan 1998; MacGregor and Jordan 1998)."

"Tamoxifen has been followed recently by newer SERMs, in particular raloxifene, that promise to provide many of tamoxifen's benefits with fewer risks (Howell, Downey et al. 1996; Gradishar and Jordan 1997; Gustafsson 1998; Jordan 1998; Purdie 1999; Sato, Grese et al. 1999). These newer SERMs, including idoxifene (Nuttall, Bradbeer et al. 1998), CP-336,156 (Ke, Paralkar et al. 1998), GW5638 (Willson, Norris et al. 1997), LY353581 (Sato, Turner et al. 1998) are part of the second- and third generation of partial estrogen agonists/antagonists. In addition, a new generation of pure antiestrogens such as RU 58,688 (Van de Velde, Nique et al. 1994) have been reported. A large number of additional partial and pure estrogen agonist/antagonist compounds and treatment modalities have reported recently (Bryant and Dodge 1995; Bryant and Dodge 1995; Cullinan 1995; Dodge 1995; Grese 1995; Labrie and Merand 1995; Labrie and Merand 1995; Thompson 1995; Audia and Neubauer 1996; Black, Bryant et al. 1996; Thompson 1996; Cullinan 1997; Wilson 1997; Miller, Collini et al. 1999; Palkowitz 1999; Wilson 1999)."

"A "***Selective Estrogen Receptor Modulator***" (or "SERM") is a compound that exhibits activity as an agonist or antagonist of an estrogen receptor (e.g., ER.alpha. or ER.beta.) in a tissue-dependent manner. Thus, as will be apparent to those of skill in the biochemistry and endocrinology arts, compounds of the invention that function as SERMs can act as estrogen receptor agonists in some tissues (e.g., bone, brain, and/or heart) and as antagonists in other tissue types, such as the breast and/or uterine lining."

United States Patent **6,245,819**

Halonen , et al. **June 12, 2001**

Title: Method for the treatment of vaginal dryness and sexual dysfunction in women during or after the menopause

"Antiestrogens, now often referred to as "SERM"s (selective estrogen receptor modulators), have both estrogen-like and antiestrogenic properties (Kauffman & Bryant, 1995)."